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2767 Ibrutinib Is Highly Active As First Line Therapy in Symptomatic Waldenstrom's Macroglobulinemia

Program: Oral and Poster Abstracts
Session: 623. Mantle Cell, Follicular, and Other Indolent B-Cell Lymphoma—Clinical Studies: Poster II

Sunday, December 10, 2017, 6:00 PM-8:00 PM
Bldg A, Lvl 1, Hall A2 (Georgia World Congress Center)

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Activating mutations in MYD88 and CXCR4 mutations are present in 95-97% and 40-45% of previously untreated patients with Waldenström's macroglobulinemia, respectively. MYD88 mutations trigger malignant cell growth through Bruton's Tyrosine Kinase and Hematopoietic Cell Kinase, both targets of ibrutinib (Yang et al, Blood 2013; Blood 2016). CXCR4 mutations confer in vitro as well as clinical evidence of resistance in previously treated WM patients to ibrutinib (Cao et al, Leukemia 2014, Treon et al NEJM 2015). Ibrutinib produces overall and major [partial response (PR) or better] responses in 90% and 70-75% of previously treated WM patients (Treon et al, NEJM 2015; Dimopoulos et al, Lancet Oncol. 2017). The activity of ibrutinib in untreated, symptomatic WM patients is not known. We therefore investigated the activity and safety of ibrutinib in this patient population. Thirty patients were enrolled in this study. Key baseline characteristics were as follows: median age 67 (range 43-83 yrs); 23 (77%) were male, IPSSWM scores were low (n=5; 17%), intermediate (n=11; 37%), and high (n=14; 47%); median serum IgM was 4,369 (range 844-10,321); median hemoglobin level was 10.3 (range 7.5-14.5 g/dL); median serum B_2M level was 3.8 (2.0-7.6 mg/L); adenopathy >1.5 cm (n=10; 33%); splenomegaly >15 cm (n=5; 17%), and median bone marrow disease involvement was 65% (range 5-95%). All patients expressed the $MYD88^{L265P}$ mutation, and 14 (47%) had a CXCR4 mutation. Patients received 420 mg a day of ibrutinib, and dose de-escalation for toxicity was permitted. The median time on therapy was 8.1 (range 2.0-16.4 months), and was similar for CXCR4 wild-type ($CXCR4^{WT}$) and CXCR4 mutated ($CXCR4^{Mut}$) patients (9.4 vs. 8.0 months, respectively p=0.98). The overall and major (>PR) response rates were 96.7% and 80%. Five (17%) patients achieved a VGPR. No complete responses were observed. At best response, median serum IgM level declined from 4,380 to 1,786 (p=0.0001). At baseline 18/30 (60%) patients had a serum IgM >3,000 mg/dL versus 2/30 (7%) patients at best response (p<0.0001). At best response, median bone marrow involvement declined from 65% to 20% (p<0.0001), with decreased or resolved adenopathy (n=7; 70%) and splenomegaly (n=4; 80%) observed in most patients with baseline extramedullary disease. The median hemoglobin level increased from 10.3 to 13.6 g/dL (p<0.0001). The impact of CXCR4 mutation status on responses and time to at least a minor (overall) and PR or better (major) response are shown in **Table 1**.

With a median follow-up of 8.1 months, two patients met progression criteria while on therapy, both of whom were CXCR4 mutated, and one of whom self-held protocol therapy >2 weeks due to travel. The latter patient continues treatment for clinical benefit per protocol. Overall, treatment was well tolerated. Grade 2 AEs: arthralgia (n=1); bruising (n=1); procedure related bleeding (n=1); hypertension (n=2); muscle cramps (n=1); neutropenia (n=3); vasculitic rash (n=1); URI (n=1); UTI (n=2). Grade 3 AEs: reversible AST/ALT elevation (n=1); foot pain (n=1); thrombocytopenia (n=1); and hypertension (n=1). Three patients (10%) had treatment-related atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=2)] and continued ibrutinib with medical management for their atrial arrhythmia. Four study patients are off protocol therapy due to progression (n=1); reversible drug-induced hepatitis (n=1); unrelated ventricular arrhythmia (n=1); and withdrawal of consent due to travel (n=1). One patient required dose reduction for vasculitic rash/foot pain (to 140 mg/day). Our findings provide the first report of activity and safety of ibrutinib in previously untreated and symptomatic patients with Waldenström's macroglobulinemia, and show that ibrutinib is highly active and well-tolerated as a single agent, with no unexpected toxicities. Delays in ibrutinib response are associated with expression of mutated CXCR4. (ClinicalTrials.gov number, NCT02604511).

Table 1.

	All Patients (n=30)	$MYD88^{L265P}CXCR^{WT}$ (n=16)	$MYD88^{L265P}CXCR4^{Mut}$ (n=14)	P-value
Overall Responses (%)	96.7	100	92.9	0.47
Major Responses (%)	80.0	87.5	71.4	0.38
Median Time to Minor Response or better (months)	1.0	0.9	1.9	0.10
Median Time to Major Response (months)	2.0	2.0	7.9	0.05

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